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(54) NEW CRYSTALLINE CEPHALOSPORIN AND PROCESSES FOR PREPARING SAME



1277 137

(71) We, ELI LILLY AND COMPANY, a Corporation organised and existing under the laws of the State of Indiana, United States of America, of 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns new cephalixin monohydrate crystals useful in formulations of the antibiotic, and processes for preparing the novel cephalixin monohydrate.

Cephalixin is a generic term used to identify a chemical compound, 7 - (D - α - amino - phenylacetamido) - 3 - methyl - 3 - cephem-4 - carboxylic acid. The antibiotic is active as a broad spectrum antibiotic effective in controlling diseases caused by a wide variety of Gram-positive and Gram-negative micro-organisms. One of the unique features of this cephalosporin is that it has shown outstanding advantages for use as an oral antibiotic.

Cephalixin is one of the semi-synthetically produced cephalosporins. Recrystallization of cephalixin, without regard to the method, whereby it is produced, from organic solvents such as acetonitrile, N,N - dimethyl - formamide, dimethylsulfoxide, methanol and ethanol, yields an anhydrous product. The anhydrous product is characteristically a small fiber-like crystal which is fluffy and bulky and hygroscopic in nature. It easily picks up a static charge, and is relatively unstable because of its hygroscopic properties. These characteristics are particularly troublesome in preparing the compound for pharmaceutical uses. The charged particles repel one another and tend to be flyaway when being weighed and when being filled into capsules. The water

absorbed because of the material's hygroscopicity, although tending to neutralize the static charge, causes the crystals to change weight and to make accurate weighing difficult.

This invention provides crystalline cephalixin monohydrate exhibiting essentially the following X-ray diffraction data:

Spacing d	Relative Intensities I/I ₁	
15.15	.40	
11.85	1.00	55
11.00	.30	
9.36	.20	
8.55	.50	
7.86	.50	
6.89	.20	60
5.98	.40	
5.39	1.00	
4.97	.50	
4.76	.40	
4.57	.40	65
4.39	.60	
4.22	.60	
4.00	.70	
3.86	.70	
3.60	.80	70
3.46	.30	
3.24	.60	
3.10	.60	
2.98	.40	
2.90	.60	75
2.81	.40	
2.73	.20	
2.68	.40	
2.63	.10	
2.47	.30	80
2.41	.15	
2.31	.30	
2.25	.30	

[Price 25p]

	Spacing d	Relative Intensities I/I ₁		
	2.12	.10	In accordance with this embodiment of the	65
	2.09	.05	process, crystalline cephalixin monohydrate is	
5	2.01	.02	prepared by precipitation from an aqueous	
	1.93	.05	solution, maintained at above 58°C. of an	
	1.87	.05	acid addition salt of cephalixin. The nature	70
	1.85	.05	of the acid salt is not a critical feature of	
10	1.82	.10	the invention, the only requirement being	
	1.72	.05	that the salt have an appreciable solubility	
	1.66	.02	in the aqueous solution at the required tem-	
	1.62	.02	perature. The precipitation of the cephalixin	
			monohydrate is accomplished by the addition	75
			of the aqueous solution of a base until the	
			pH of the solution is in the range of pH	
			3.5 to about pH 7, within which pH range	
			cephalexin exists in its zwitterion form. The	
15			nature of the base employed is similarly, not	80
			critical. In order to simplify the purification	
			of the cephalixin monohydrate, however, it	
			is preferred that the base employed is one	
20			which forms a water soluble salt with the	
			acid employed in the formation of the	85
			cephalexin salt.	
			As illustrative of this embodiment of the	
25			invention, cephalixin, as prepared, for	90
			example, by any of the hereinbefore disclosed	
			methods, is purified by suspending the anti-	
			biotic or a salt thereof in an aqueous solution	
			containing sufficient quantity of a strong acid	
			(as hereinafter described) to dissolve the anti-	
30			biotic at above 58°C.; adding a water soluble	95
			base to precipitate the cephalixin as its mono-	
			hydrate; separating the crystalline cephalixin	
			monohydrate by, for instance, filtration or de-	
			contation. The temperature of the solution	
35			may be raised to 58°C. at any stage prior	100
			to addition of the water soluble base. Raising	
			the temperature to 58°C. prior to suspension	
			of the antibiotic, for instance, eliminates the	
40			need for heating the acidic solution of the	105
			antibiotic and thereby minimizes the time	
			during which the antibiotic is in contact with	
			hot acid. As a further alternative, a solid,	
45			water soluble acid addition salt of cephalixin	110
			can be dissolved in an aqueous solution, the	
			solution brought to the required temperature,	
			and precipitation effected by the addition of	
			base.	
			The saturated supernatant solution contain-	
50			ing crystalline cephalixin monohydrate can be	115
			cooled to below 58°C., as for example to	
			room temperature, without transforming the	
			already formed monohydrate crystalline form	
			to the undesirable dihydrate crystalline form	
55			which crystallizes from saturated aqueous solu-	
			tions at temperatures below 58°C.	
			The aqueous medium employed in the process	120
			can be water alone, or it can contain	
			certain non-interfering water-miscible organic	
60			materials to aid in the dissolution of the anti-	125
			biotic. Such non-interfering water miscible	
			organic materials can include, illustratively,	
			lower-alkanols, as for example methanol,	
			ethanol and propanol; dilower-alkyl ketones	
			as for example acetone and methyl ethyl	

and being dense, stable, non-hygroscopic crystals.

The invention further provides a process for the preparation of cephalixin monohydrate which comprises treating an aqueous solution of a cephalixin acid addition salt at a temperature of at least 58°C. and below a temperature of 75°C. above which causes rapid decomposition of cephalixin occurs, with sufficient water-soluble base to convert the cephalixin salt to cephalixin in its zwitterion form thereby precipitating crystalline cephalixin monohydrate and separating the cephalixin monohydrate so produced from the aqueous medium.

A further provision of the invention is a process of preparing cephalixin monohydrate which comprises comingling cephalixin with 20 to 50 percent of its dry weight of water at room temperature and drying the resulting crystalline cephalixin monohydrate to 4 to 8 percent by weight water content.

The novel crystalline form of cephalixin of this invention has the unique X-ray diffraction properties stated above, at $\lambda=1.5405$ using a Cu: Ni 45 Kv. 20 ma. radiation.

The crystals are large in form, extremely dense, non-hygroscopic, and do not pick up a static charge. These characteristics afford a considerably greater ease in pharmaceutical formulating operations and are admirably adapted for formulation, particularly into solid dosage forms, such as filled capsules.

In addition to having characteristics which make possible its use directly in formulating operations, the crystalline monohydrate can be vacuum dried at elevated temperatures, as for example at 60°C. or above, to yield an anhydrous powder with the same crystalline form and advantageous properties possessed by the monohydrate. The new form of crystalline anhydrous cephalixin is also suitable for the formulation of pharmaceutical compositions containing cephalixin.

In accordance with one embodiment of the process of this invention, the crystalline cephalixin monohydrate hereinbefore described is obtained from cephalixin or from any of the acid addition salts thereof, as for example the hydrochloride, sulfate, nitrate, phosphate, or hydrobromide salt.

In accordance with this embodiment of the process, crystalline cephalixin monohydrate is prepared by precipitation from an aqueous solution, maintained at above 58°C. of an acid addition salt of cephalixin. The nature of the acid salt is not a critical feature of the invention, the only requirement being that the salt have an appreciable solubility in the aqueous solution at the required temperature. The precipitation of the cephalixin monohydrate is accomplished by the addition of the aqueous solution of a base until the pH of the solution is in the range of pH 3.5 to about pH 7, within which pH range cephalixin exists in its zwitterion form. The nature of the base employed is similarly, not critical. In order to simplify the purification of the cephalixin monohydrate, however, it is preferred that the base employed is one which forms a water soluble salt with the acid employed in the formation of the cephalixin salt.

As illustrative of this embodiment of the invention, cephalixin, as prepared, for example, by any of the hereinbefore disclosed methods, is purified by suspending the antibiotic or a salt thereof in an aqueous solution containing sufficient quantity of a strong acid (as hereinafter described) to dissolve the antibiotic at above 58°C.; adding a water soluble base to precipitate the cephalixin as its monohydrate; separating the crystalline cephalixin monohydrate by, for instance, filtration or decantation. The temperature of the solution may be raised to 58°C. at any stage prior to addition of the water soluble base. Raising the temperature to 58°C. prior to suspension of the antibiotic, for instance, eliminates the need for heating the acidic solution of the antibiotic and thereby minimizes the time during which the antibiotic is in contact with hot acid. As a further alternative, a solid, water soluble acid addition salt of cephalixin can be dissolved in an aqueous solution, the solution brought to the required temperature, and precipitation effected by the addition of base.

The saturated supernatant solution containing crystalline cephalixin monohydrate can be cooled to below 58°C., as for example to room temperature, without transforming the already formed monohydrate crystalline form to the undesirable dihydrate crystalline form which crystallizes from saturated aqueous solutions at temperatures below 58°C.

The aqueous medium employed in the process can be water alone, or it can contain certain non-interfering water-miscible organic materials to aid in the dissolution of the antibiotic. Such non-interfering water miscible organic materials can include, illustratively, lower-alkanols, as for example methanol, ethanol and propanol; dilower-alkyl ketones as for example acetone and methyl ethyl

ketone; and lower-alkanoic acids, as for example acetic acid and propionic acid.

Examples of strong acids to dissolve cephalixin in water prior to performing the process of this invention include mineral acids, as for example hydrochloric, nitric, phosphoric, hydrobromic, and sulfuric acids, or strong organic acids, as for example benzenesulfonic acid, toluenesulfonic acid, p - chlorobenzene - sulfonic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, cyclohexanesulfonic acid, toluic acid or o - chlorobenzoic acid.

Precipitation is accomplished by the addition of any basic substance which is soluble in water and which forms a water soluble salt with the anion of the cephalosporin salt. Such bases can include sodium hydroxide, potassium hydroxide, magnesium hydroxide, lithium hydroxide, ammonium hydroxide, methylammonium hydroxide, dimethylammonium hydroxide, trimethylammonium hydroxide, ethylammonium hydroxide, diethyl - ammonium hydroxide, methylethylammonium hydroxide, dimethylethylammonium hydroxide, diethylmethylammonium hydroxide, isopropylamine, dimethylisopropylamine, β - hydroxyethylamine and ethylene diamine.

The temperature of the precipitation step must be at or above 58°C. Aqueous acidic solutions of cephalixin precipitated by the addition of base at below this temperature yield a dihydrate which is efflorescent and unstable. Temperatures greatly in excess of 58°C. cause a more rapid decomposition of the antibiotic and are to be avoided. The optimum precipitation temperature is 60°C. to 75°C.

In accordance with another process embodiment of this invention, the hereinbefore described crystalline cephalixin monohydrate is obtained from cephalixin. In this embodiment, cephalixin is placed in a large rotating vessel and 20 to 50% by weight of water is added. This amount of water does not form an appreciable aqueous phase or cause slurring to occur.

Optionally, the mixture is allowed to tumble in this rotating vessel for one or more hours at about ambient room temperature to effect complete conversion to the monohydrate crystalline form. The mixture is then subjected to vacuum drying to 4 to 8 percent by weight concentration.

The addition of a substantially lesser amount of water is to be avoided as it could result in incomplete conversion to the monohydrate crystalline form; a greater amount will cause slurring and make drying difficult.

The operability of this method to effect the modification of the crystal structure of cephalixin is unexpected and surprising since the exposure of cephalixin to a humid atmospheric condition will hydrate the molecule forming a mixture of mono- and dihydrate

without the concomitant change in crystal structure. Cephalixin hydrated by exposure to moist air does not lose its tendency to pick up a static charge and become flyaway.

The following examples will further illustrate the processes of this invention.

EXAMPLE I

Cephalixin, 15 g., is suspended in 100 ml. of water at room temperature. Concentrated hydrochloric acid is added dropwise in an amount just sufficient to dissolve the antibiotic (90—100 drops). The acidity of the resulting solution is pH 1.8—1.9. The solution is heated to about 60°C. by immersion in a steam bath, and concentrated ammonium hydroxide is then added fairly rapidly with stirring to pH 4.3. After the addition of ammonium hydroxide is complete, the crystalline cephalixin monohydrate which has been precipitated is isolated by filtration and the product is washed with a small amount of water to remove any coprecipitated ammonium chloride.

EXAMPLE II

The procedure of Example I is followed except that the antibiotic is first suspended in water at a temperature of 65°C. before the acid is added to effect dissolution.

EXAMPLE III

The procedure of Example II is followed except that glacial acetic acid is added to dissolve the suspended cephalixin.

EXAMPLE IV

Cephalixin (17.43 kg.) was placed in a Devine rotary jacketed drier. Recirculatory water at 20°C. was passed through the jacket during the hydration procedure. Rotation was begun and deionized water (6.97 l.) was added as a fine spray from a pressurized vessel over a one hour period. Rotation was discontinued and the interior of the drier was scraped down. A vacuum was applied to the drier for two hours without stirring and then released.

The whole mixture was allowed to stand at room temperature in the drier for 18 hours. Rotation was then begun and the temperature of the vessel was raised to 30°C. A vacuum was applied to the vessel for 12 hours until the vessel had attained an internal pressure or 8 mm. Hg. at an internal temperature of 30°C. The sample of cephalixin monohydrate was then ground in a Fitzpatrick mill prior to formulating.

WHAT WE CLAIM IS:—

1. Crystalline cephalixin monohydrate exhibiting essentially the following X-ray diffraction data:

ketone; and lower-alkanoic acids, as for example acetic acid and propionic acid.

Examples of strong acids to dissolve cephalixin in water prior to performing the process of this invention include mineral acids, as for example hydrochloric, nitric, phosphoric, hydrobromic, and sulfuric acids, or strong organic acids, as for example benzenesulfonic acid, toluenesulfonic acid, p - chlorobenzene - sulfonic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, cyclohexanesulfonic acid, toluic acid or o - chlorobenzoic acid.

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WHAT WE CLAIM IS:—

1. Crystalline cephalixin monohydrate exhibiting essentially the following X-ray diffraction data:



	Spacing d	Relative Intensities I/I ₁	temperature of at least 58°C. and below a temperature of 75°C. with sufficient water-soluble base to convert the cephalixin salt to cephalixin in its zwitterion form thereby precipitating crystalline cephalixin monohydrate and separating the cephalixin monohydrate so produced from the aqueous medium.	
5	15.15	.40		55
	11.85	1.00		
	11.00	.30		
	9.36	.20		
	8.55	.50		60
	7.86	.50		
10	6.89	.20		
	5.98	.40		
	5.39	1.00		
	4.97	.50		65
	4.76	.40		
15	4.57	.40		
	4.39	.60		
	4.22	.60		
	4.00	.70		70
	3.86	.70		
20	3.60	.80		
	3.46	.30		
	3.24	.60		
	3.10	.60		75
	2.98	.40		
25	2.90	.60		
	2.81	.40		
	2.73	.20		
	2.68	.40		
	2.63	.10		80
30	2.47	.30		
	2.41	.15		
	2.31	.30		
	2.25	.30		
	2.12	.10		85
35	2.09	.05		
	2.01	.02		
	1.93	.05		
	1.87	.05		90
	1.85	.05		
40	1.82	.10		
	1.72	.05		
	1.66	.02		
	1.62	.02		95

45 and being a dense, stable, non-hygroscopic crystal.

2. A pharmaceutical composition comprising the monohydrate defined in claim 1 and a solid or liquid carrier.

50 3. A process for the preparation of the cephalixin monohydrate according to claim 1, which comprises treating an aqueous solution of a cephalixin acid addition salt at a

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